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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/485,879 | 06/22/2000 | MICHAEL GIESING | 790076.401 | 6896 |

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SEED INTELLECTUAL PROPERTY LAW GROUP
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| EXAMINER | |
|---|---|
| GOLDBERG, JEANINE ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/485,879 | GIESING ET AL. | |
| | Examiner | Art Unit | |
| | Jeanine A Goldberg | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22,24-39 and 44-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24-39 and 44-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is in response to the papers filed July 6, 2004. Currently, claims 22, 24-39, 44-63 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 6, 2004 has been entered.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's response and the amendments to the claims. The action contains new grounds of rejection necessitated by amendment.

### *Priority*

4. This application is a 371 of PCT/EP/98/05360, filed August 24, 1998. This application also claims priority to foreign document 197 36 691.0, filed August 22, 1997, however, a translation of this document has not been provided.

Applicant's request clarification from the Examiner regarding the reference to the priority document in the first paragraph. The examiner has not required or even requested a translation. The examiner has merely indicated that the translation has not been provided.

## ***New Grounds of Rejection Necessitated by Amendment***

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 22, 24-28, 32, 36-37, 44-45, 49-51, 54-59, 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditkoff et al. (Surgery, Vol. 120, December 1996, pages 959-965) in view of Duffy (US Pat. 5,871,917, February 1999) in view of Hoon et al (US Pat 6,057,105, May 2, 2000).

Ditkoff et al. (herein referred to as Ditkoff) teaches a method of detecting circulating thyroid cells in peripheral blood. Ditkoff teaches that the tissue specificity of thyroglobulin gene expression and the sensitivity of RT-PCR analysis make detection of thyroglobulin detection useful. Postoperative peripheral blood was sampled. Thyroglobulin transcripts were detected in all 9/9 patients with metastatic thyroid cancer. 0/6 patients with benign thyroid disease and 0/7 normal volunteers. Ditkoff teaches that RT-PCR can be used to detect thyroglobulin mRNA in peripheral blood since the presence of these transcripts correlate with the existence of extrathyroidal disease. As specifically taught in the methods section, blood was taken from patients/volunteers and total RNA was extracted, RT-PCR was carried out. This step of investigating takes place without previous removal of cancer cells from the plurality of cells (limitation of Claim 61ai). Further, the thyroglobulin gene is a nucleic acid which is essentially not expressed in a non-cancer cell in the body blood. For example, since thyroglobulin is secreted exclusively by the thyroid follicular cells, thyroglobulin is not expressed by neutrophils (i.e. a non-cancer cell in the blood)(limitations of Claim 61aii). As seen in

the Table, it is clear that no control or benign thyroid disease patients showed any RT-PCR. Therefore, the ordinary artisan would have clearly recognized that the RT-PCR method of Ditkoff would be a technique that may be used to identify blood-borne tumor cells. Ditkoff further teaches that RT-PCR has been used to identify blood-borne tumor cells in several solid cancers including melanoma, prostate and neuroblastoma (page 964, col. 1).

Duffy teaches methods of identifying differentially methylated and mutated nucleic acids relative to the corresponding DNA from normal cells. In Example 1, Duffy teaches that DNA was isolated from two different types of cells from patients who have chronic lymphocytic leukemia (CLL)(col. 21, lines 19-22). The CD5+ cells can be isolated by highly specific antibodies in a FACs (fluorescence activated cell sorter). Duff thus teaches isolating cancer cells from non-cancer cells using FACs. Duffy also teaches that three probes gave methyl-differential displays in breast cancer and their matched normal controls isolated from three individual patients (col. 21, lines 33-37). DNA isolated from malignant B-cells and neutrophil cells was performed. Mononuclear and neutrophil cells were isolated from the peripheral whole blood of CLL patients by Ficoll/Hypage centrifugation. Leukemic B-cells (CD5+) were sorted from mononuclear cells in the presence of fluorescent anti-CD5 antibodies by FACs (col. 21, lines 40-48). Duffy teaches that after the cells was separated the DNA from leukemic B-cells was used as the tester and the DNA from neutrophil cells was used as the driver. Thus, probes were found that were differentially expressed in normal and cancer cells. Therefore the method of Duffy teaches isolated from blood cancer CD5+ cells from

normal neutorphils and investigating the relative presence of positive clones identified by the MDD method. Genomic DNA isolated from cancer tissues and their respective matched normal tissues were analyzed. The CLL58 probe was isolated and further tested by hybridization to the malignant B-cell and neutrophil cell DNA. The analysis revealed that a larger fragment was much less intensely hybridized than a lower molecular weigh fragment in the malignant B-cell DNA, while the neutrophil cell DNA was just the opposite result (col. 25, lines 37-40). Therefore both normal and cancerous cells were isolated and investigated (limitations of Claim 61 b, c, d). Similarly, Duffy specifically teaches that detection by BR50 in ovarian cancers was analyzed to determine whether the same hypomethylation phenomena happens. Duffy teaches taking samples from primary ovarian cancer tissue, metastatic tumor tissue and matched normal tissue. The expression patters illustrates that using BR50, tumor related hypomethylation events may be detected (col. 27, lines 10-30).

Additionally, Hoon et al. (herein referred to as Hoon) teaches methods of using multiple cancer makers provide increased sensitivity over methods using single cancer markers. Hoon teaches the prior art was limited by their ability to discriminate cancer cells from normal cells also carrying the marker, thus reducing the specificity and reliability. Hoon teaches that "tumor, heterogeneity has caused sensitivity problems where a single-specific marker has been employed" (col. 2, lines 23-29). Hoon provides a list of makers which are preferably detected, including tyrosinase, MAGE3, Cytokenatin 20 (col. 3, lines 15-30). Hoon teaches that the method is conducted at least twice on a given sample using at least two different primer pairs specific for two

different specific markers (col. 4, lines 37-40). In a specific example, 15ml of blood was obtained from patients and collected in 5 sodium citrate tubes (col. 19, lines 22-23). The tubes were centrifuged and the buffy coat was removed. Analysis was performed on the blood specimens by PCR using multiple markers. The use of more than one marker can verify the presence of occult melanoma cells and significantly increase the sensitivity of detecting melanoma cells that express few or no copies of tyrosinase mRNA (col. 21, lines 60-65).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have combined the methods of Ditkoff and Duffy because Hoon teaches that detection of multiple cancer makers provide increased sensitivity over methods using single cancer markers. Therefore, the ordinary artisan would have been motivated to have combined several cancer detection methods for several markers to increase sensitivity. The methods of Ditkoff and Duffy both are directed to methods which allow detection of cancer-associated or cancer-specific markers within a body fluid, namely blood, which indicates an increased risk for or the presence of a disseminated cancer cell. The method of Ditkoff detects amplification without the need for enrichment, whereas the method of Duffy isolates cancer cells and normal cells and subsequently performs differential expression analysis. The collection of two tubes of blood from a cancer patient or a patient suspected of having cancer and performing the analysis of both Ditkoff and Duffy allows for the detection of multiple markers which increases sensitivity and increases the likelihood of early detection of cancer, as taught by Hoon. There are numerous reasons why it is advantageous to use peripheral blood including

that it is less stressful for the patient and therefore may be performed on a routine basis together with other laboratory tests. Therefore, when blood is drawn from a patient having cancer or suspected of having metatstasis, several tubes may be collected with minimal discomfort or stress for the patient. The multiple tubes of blood may be used for a variety of laboratory tests including RT-PCR and cancer cell isolation. As specifically provided by Hoon, detection of more than a single cancer marker is strongly recommended to provide more sensitive and accurate results. Therefore, analyzing a single patients blood samples for more than one known cancer marker would have the expected benefit of minimizing the stress and pain inflicted on the patient while simultaneously obtaining sensitive and meaningful results to determine whether micrometastasis is present in the sample.

7. Claims 29-31, 33-35, 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditkoff et al. (Surgery, Vol. 120, December 1996, pages 959-965) in view of Duffy (US Pat. 5,871,917, February 1999) in view of Hoon et al (US Pat 6,057,105, May 2, 2000) as applied to Claims 22, 24-28, 32, 36-37, 44-45, 49-51, 54-59, 61-63 above and further in view of Schmitz et al. (US Pat. 6,190,870, February 20, 2001).

Neither Ditkoff nor Duffy nor Hoon specifically teach the analysis of oncogenes, tumor suppressor genes, or other specifically recited genes.

However, Schmitz et al (herein referred to as Schmitz) teaches that tumor cells, particularly carcinoma cells are separated from peripheral blood by magnetic sorting (abstract). Specifically Schmitz teaches that cell samples may be contacted with

antibodies which are directed to tumor antigens or lineage specific antigens are used to magnetically label the tumor cells. The labeled cells are separated from unlabeled hematopoietic cells by magnetic separation. The fraction of cell enriched for tumor cells is useful for quantitating the tumor cells and as a source of tumor cells for further characterization (col. 3, lines 30-45). Schmitz provides a long list of separation markers which may be cell surface antigens or located in the cytoplasm of the tumor cells. These markers include EMA, HEA-125, C26, among many others (col. 4). Moreover, Schmitz teaches that tumor cells may be further characterized as to their phenotype by PCR, FISH in situ FISH competitive hybridization (col. 9, lines 4-6). Moreover, the expression of a number of proteins related to malignancy is of interest including oncogenes, erbB, myc, p53, drug resistance proteins, metatstic factors including metalloproteases, integrins, angiogenic factors and others (col. 9, lines 8-15)(limitations of Claims 33-36).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ditkoff or Duffy or Hoon with the teaching of Schmitz that certain markers are of interest in cancer. Schmitz teaches numerous genes which are differentially expressed between cancer and normal cells, such that the ordinary artisan would be motivated to have selected any combination of such markers depending upon the suspected form of cancer in which they are studying or select a combination which is more general to cancers generically.

8. Claims 38-39, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsuhashi (US Pat. 5,976,797) in view of Ditkoff et al. (Surgery, Vol. 120, December 1996, pages 959-965) in view of Duffy (US Pat. 5,871,917, February 1999) in view of Hoon et al (US Pat 6,057,105, May 2, 2000) as applied to 22, 24-28, 32, 36-37, 44-45, 49-51, 54-59, 61-63 above.

Neither Ditkoff nor Duffy nor Hoon teach analyzing and identifying an anticancer therapy by administering an anticancer therapy to samples, and detecting the presence or expression of markers before and after to evaluate an anticancer therapy.

However, Mitsuhashi teaches a method for determining the cytoxoic effect of a compound by adding said compound to a sample, measuring mRNA present in sample and evaluating the cytotoxic effect of the compound. Mitsuhashi teaches studying vinblastine, cisplatin and mitomycin C.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Mitsuhashi for detecting cytotoxic effects of a anticancer compound such as cisplatin, for example, by detecting multiple markers in enriched and unenriched cultures. The ordinary artisan would have been motivated to have analyzed more than one mRNA for the reasons of specificity and reliability provided by Hoon. Determining the effect of an anticancer compound, or any compound, is accomplished by testing the nucleic acid expression prior to the administration of the compound, administering the compound and then comparing the expression following the compound administration. Therefore, the claimed methods are not novel with respect to the means in which an anticancer therapy is analyzed.

***Conclusion***

**9. No claims allowable over the art.**

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

**Jeanine Goldberg**
**Patent Examiner**
September 16, 2004